

Claims

We claim:

1. An es dendritic cell.
2. The cell of claim 1, which is genetically modified.
3. The cell of claims 1 or 2, which is immature.
4. The cell of claims 1 or 2, which is mature.
5. A genetically modified immature dendritic cell which is capable of maturation.
6. The cell of any one of the preceding claims, which is human.
7. The cell of any one of the preceding claims, which is lymphoid.
8. The cell of any one of claims 1 to 6, which is myeloid.
9. The cell of any one of the preceding claims, which is primary.
10. The cell of any one of the preceding claims, which is isolated or substantially pure.
11. The cell of any one of the preceding claims, which expresses one or more heterologous gene(s).
12. The cell of claim 11, wherein the heterologous gene(s) encode a protein which has an immunomodulatory effect.

13. The cell of claim 11, wherein the protein is a cell surface receptor.
14. The cell of claim 11, wherein the protein is Fas-ligand.
15. The cell of claim 11, wherein the gene expresses a dominant negative form of an endogenous protein.
16. The cell of claim 11, wherein the protein is an antigen target for the immune system, such as, for example, an autoantigen, a tumor antigen, or a foreign antigen for example a microbial or viral antigen.
17. The cell of any one of claims 11 to 16, wherein the cell co-expresses two or more heterologous genes.
18. The cell of claim 17, wherein one of the heterologous genes prolongs the life-span of the cell.
19. The cell of claim 18, wherein the gene is an anti-apoptotic gene.
20. The cell of claim 18 or 19, wherein the gene encodes FLIP or bcI-2.
21. The cell of any one of the preceding claims in which one or more endogenous gene(s) have been inactivated.
22. The cell of claim 21, wherein the inactivated endogenous gene(s) comprise any of: 1371, IL-12, the p35 or p40 subunit of IL-12.
23. A composition comprising the cell of any one of the preceding claims.

24. The composition of claim 23, which is a pharmaceutical composition.
25. The composition of claim 23 or 24, further comprising a pharmaceutical excipient.
26. The cell of any one of the preceding claims, for use in therapy or prophylaxis.
27. Use of the cell of any one of the preceding claims, for the manufacture of a medicament for use in therapy or prophylaxis.
28. A process for the manufacture of a medicament for use in therapy, characterized in the use, as an essential constituent of said composition, of the cell of any one of claims 1 to 22.
29. The cell of any one of claims 1 to 26, use of claim 27 or process of claim 28 wherein the therapy or prophylaxis is immunotherapy.
30. The invention of claim 29, wherein the immunotherapy comprises immunostimulation.
31. The invention of claims 29 or 30, wherein the immunostimulation comprises tumor immunotherapy or vaccination against infectious agents.
32. The invention of claim 29, wherein the immunotherapy comprises down-modulation of a detrimental immune response.
33. The invention of claim 32, wherein the down-modulation of a detrimental immune response is in the treatment of autoimmune disease or allograft rejection.
34. The invention of claim 29, wherein the immunotherapy comprises altering dendritic cell function.

35. The invention of claims 29 or 34, wherein the immunotherapy comprises inducing a Th1 to Th2 immune deviation, such as, for example, in the treatment of autoimmune diseases and disorders.

36. A method for producing dendritic cells, comprising the steps of:

- i) providing a population of embryonic stem cells;
- ii) culturing the embryonic stem cells in the presence of a cytokine or combination of cytokines which bring about differentiation of the embryonic stem cells into dendritic cells; and
- iii) recovering the dendritic cells from the culture.

37. The method according to claim 36, wherein the cytokine or combination of cytokines is or includes IL-3.

38. The method according to claim 37, wherein a combination of cytokines including IL-3 and GM-CSF is used.

39. The method according to any one of claims 36 to 38, wherein the embryonic stem cells in

- i) are in the form of embryoid bodies.

40. The method according to any one of claims 36 to 38, wherein the embryonic stem cells are genetically modified.

41. The method according to claim 40, wherein the embryonic stem cells are transfected with at least one gene which is expressed in the dendritic cells.

42. The method according to claim 41, wherein the gene is under the control of a promoter which initiates or upregulates gene expression on maturation of dendritic cells, such as the CDllc promoter.

43. The method according to claims 41 or 42, wherein the gene is a reporter gene which expresses a detectable product in the dendritic cells.
44. The method according to claim 43, wherein the gene encodes a fluorescent product.
45. The method according to claim 44, wherein the gene is the GFP gene.
46. The method according to claims 41 or 42, wherein the gene expresses a protein which has an immunomodulatory effect.
47. The method according to claim 46, wherein the protein is a cell surface receptor.
48. The method according to claim 47, wherein the protein is Fas-ligand.
49. The method according to claim 46, wherein the gene expresses a dominant negative form of an endogenous protein.
50. The method according to claim 46, wherein the protein is an antigen target for the immune system, such as an autoantigen, a tumor antigen, or a foreign antigen for example a microbial antigen.
51. The method according to claim 40, wherein the ES cells are genetically modified so as to inactivate at least one copy of at least one gene, for example by homologous recombination or antisense technology.
52. The method according to claim 51, wherein the inactivated gene is a gene normally involved in dendritic cell function, such as a gene encoding the p35 or p40 subunit of IL-12.
53. The method according to any one of claims 36 to 52, wherein the ES cells contain a gene which functions to prolong the lifespan of dendritic cells, such as the gene encoding bcl-2 or FLIP.

54. The method according to any one of claims 36 to 53, wherein the recovered dendritic cells are substantially pure.
55. The method according to any one of claims 36 to 54, wherein the ES cells are derived from a mouse strain such as CBA/Ca or C5781/6.
56. The method according to claim 55, wherein the ES cells are from the ESF116 cell line.
57. Dendritic cells produced by or obtainable by, the method according to any one of claims 36 to 56.
58. A population of embryonic stem cells for use in the method according to any one of claims 36 to 56.
59. A population of genetically modified embryonic stem cells in which a gene normally expressed in dendritic cells has been inactivated.
60. A population of genetically modified embryonic stem cells transfected with a nucleic acid comprising a promoter operably linked to a coding sequence, wherein the promoter initiates or upregulates expression of the coding sequence on maturation of dendritic cells.
61. A method for investigating a mammalian gene, which method comprises generating a test population of dendritic cells from a population of embryonic stem cells and comparing the test dendritic cells to a population of control dendritic cells which differ from the test dendritic cells in respect of the gene.

62. A process for producing a pharmaceutical composition, (*e.g.*, an immunotherapeutic composition) comprising the steps of:

- (a) providing a test system comprising the cell of any one of claims 1 to 22, or a component thereof;
- (b) providing candidate drugs;
- (c) screening the candidate drugs by contacting the test system with one of the candidate drugs and analyzing the interaction of the candidate drug with the test system, wherein the nature of the interaction is an index of pharmaceutical activity; and optionally
- (d) synthesizing or purifying a drug having pharmaceutical activity on the basis of the identity of the candidate drug screened in step (c).

63. A process for screening candidate drugs for pharmaceutical activity (*e.g.*, immunotherapeutic activity, comprising the steps of:

- (a) providing a test system comprising the cell of any one of claims 1 to 22, or a component thereof;
- (b) providing candidate drugs;
- (c) screening the candidate drugs by contacting the test system with one of the candidate drugs and analyzing the interaction of the candidate drug with the test system, wherein the nature of the interaction is an index of pharmaceutical activity.